Using Large Scale, Multi-cellular Pathway Modeling To Understand Cellular Differentiation

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1. Modeling Cellular Differentiation

Development of a biological system from one state to another in a controlled manner usually involves feedback to assert such control. The multi-cellular network controlling tissue differentiation in the common fruit fly, *Drosophila sp*., is no exception. [3, 4, 5] During *Drosophila's* development a series of bands develop along the major axis of the growing embryo (see micrograph in figure 6). Such bands are a graphical indicator of the underlying cellular differentiation in progress. The schematic shown on the right, figure 1, represents the control network responsible for cellular differentiation in *Drosophila*. [3] Though complex, this network typically bifurcates into one of three states. If a cell is producing the gene product wg then the protein WG will likely be produced as well. The WG protein is exported into the cellular environment and picked up by neighboring cells where it can promote the expression of the gene product en. The en gene product represses the production of wg and puts the cell into a different state from a cell producing WG, specifically into a state where it is producing and expressing HH. Thus, cells will typically be producing either WG or HH with a small percentage of cells producing low levels of both of these proteins.

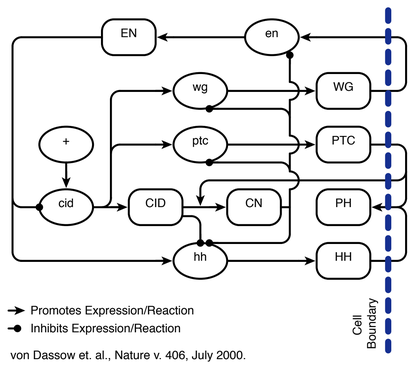

Figure 1: Developmental control circuit derived by Dassow. [3] Lower case letters are mRNA (gene products) while upper case letters denote proteins. Arrows indicate places where a compound promotes the production of another compound while filled circles denote places where a compound represses the production of another species.

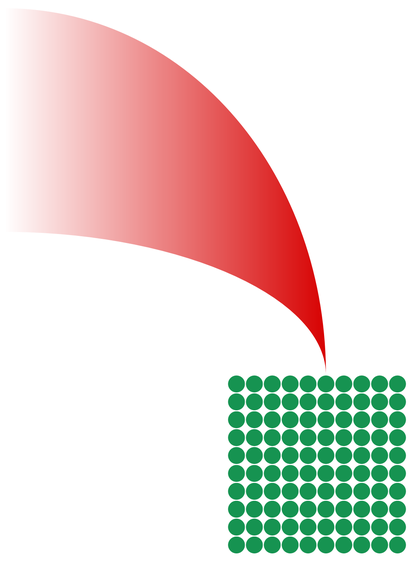

Figure 2: The 10 by 10 grid of cells used for multi-cellular simulations. The circuit of figure 1 is embedded in each cell and all cells are connected to each other through a diffusion limited environment.

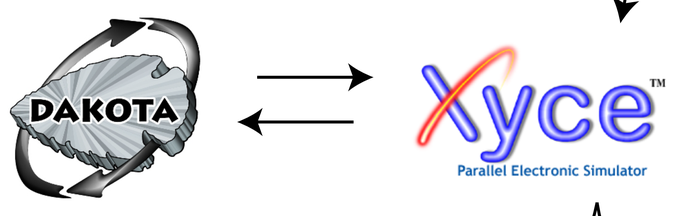

Figure 3: The circuit simulation program Xyce conducts the transient simulation of cellular development while Dakota directs the model parameter sampling protocol. Together the programs allow one to methodically explore and understand the parameter phase space for a complex model.

2. Implementation

Actual simulations of the *Drosophila* network were carried out as follows. The network was converted to an electrical circuit using analogs for chemical reactions, material storage, promotion, repression, degradation and diffusion. These analogs treat electrical charge, a conserved quantity in electrical circuit simulators as mass. Once the intracellular circuit was created, a 10 by 10 grid of cells embedded within a diffusion limited environment was created, again as a circuit. Fundamental constants like reaction rates, enzymatic turnover rates and diffusion coefficients were parameterized within this circuit. Such parameterization allows the optimization program Dakota to alter parameters between simulation runs to explore the phase space for this system.

3. Understanding Large Parameter Spaces

With expression, enzymatic turn-over, reaction and diffusion rates and noise levels all parameterized, a design of experiments approach with latin-hypercube sampling was used to understand how this collection of state variables controls the resulting system. To address the 22 primary model parameters, over 50,000 simulation runs were coordinated by Dakota and conducted by Xyce using a multi-level parallel computation approach. A statistical analysis of the simulation output allows one to gauge dominate control parameters and system stability relative to initial condition noise.

4. Successful Differentiation

Shown below in figure 4 are concentration contour plots of the species WG and HH. Initially, the system was started with zero concentration of the exported species, PH, PTC and HH and an oscillatory level of WG. This initial oscillatory state represents the initial bias that anterior-posterior, dorso-ventral patterning hierarchies initiate in the developing embryo. [4] Additionally, a 10% rms. random noise was added to the WG initial conditions to simulate disturbances of the system from an ideal starting state. Such noise was also parameterized in the circuit and varied to gauge system robustness. Physically, the striations in concentration shown in figure 4 represent layers of cells becoming WG producing or HH producing over time similar to the micrograph of a *Drosophila* embryo shown in figure 6.

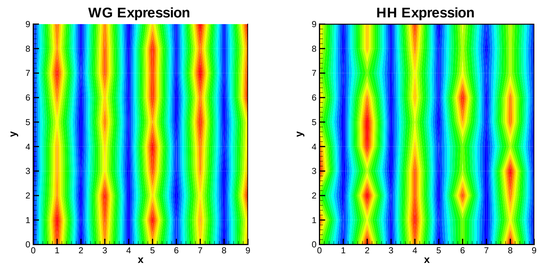

Figure 4: A 10 by 10 grid of cells starting with an initial noisy, oscillatory level of WG differentiates into WG producing and HH producing populations. The plot on the left depicts 5 layers of WG producing cells while the right contour plot depicts 5 layers of HH producing cells at the same time point. Initially the system was started with 10% rms. random noise in WG superimposed over the initial conditions.

5. Sensitivity to Noise

To study the effect of initial noise on the system's ability to differentiate, simulations were started with varying amounts of random noise in the WG concentration field. This noise was gaussian in distribution and ranged from 0 to 30% of the maximal value of WG. Figure 5 shows the probability of successful cellular differentiation as a function of initial system noise. While this system is very stable in the absence of noise [3, 5], this work demonstrates that even a small quantity of initial noise significantly reduces the system's functionality.

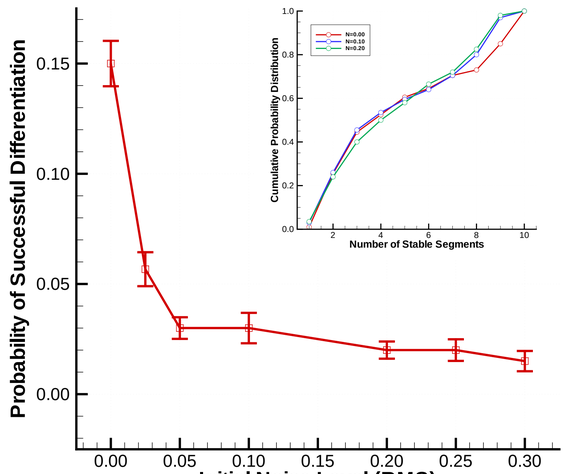

Figure 5: Noise in the initial WG concentration field significantly reduces the probability of successful differentiation. As shown in the inset, the cumulative probability for producing fewer than eight body segments (a failure to differentiate) increases as noise is added to the system.

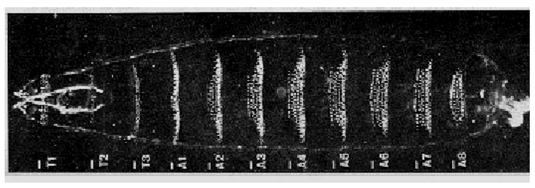

Figure 6: Micrograph of a Drosophila embryo. [9] Note the bands of differentiating cells perpendicular to the central axis.

Conclusions

Though still in development, this biological circuit simulator has the potential to handle large and complex problems. Depending on the type of data available, one can cast problems as digital or analog circuits and easily simulate many replicas of a single circuit interacting with a collection of other circuits. Through the coupling to an optimization program, one can explore the dynamics of multiple cellular networks or of entire cell cultures elucidating governing parameters as well. Here multi-cellular coupling demonstrated that the *Drosophila* differentiation network is very sensitive to initial noise.

References
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